Editorial

Immunoglobulins in the lung

The lungs are continually exposed to a vast range of antigenic material. The immunoglobulins of the lung therefore have an important role in the neutralisation of antigens, which leads to cellular processing and removal. The lung is undoubtedly a major "immunological organ" since it contains a considerable amount of lymphoid tissue, with the ability to synthesise immunoglobulins. The analysis of immunoglobulins in the secretions of the lung has clarified our understanding of their origins in this organ but the details of the functions of immunoglobulins in the lung are not well understood. Nevertheless, the secretions lining the airways are likely to be the site where lung immunoglobulin function as a front line of defence is most important. For this reason we can be fairly confident that studies of immunoglobulins in lung secretions will be relevant to their significance in vivo.

Origins of immunoglobulins in lung secretions

So far our knowledge of the origins of the immunoglobulins in lung secretions has resulted almost entirely from the development of antisera that are specific for the immunoglobulins and their discrete subpopulations, such as the structural forms of IgA and the immunoglobulin subclasses. These antisera have been used for immunohistochemical studies, which have shown the presence of immunoglobulin bearing plasma cells in the bronchial mucosa and in the secretions of the airways, thus confirming that local synthesis of immunoglobulins does occur at these sites. Furthermore, the development of specific and sensitive immunological assays has allowed the immunoglobulin composition of lung secretions to be studied in some detail.

In essence, there are two major sources of immunoglobulins in the lung secretions:

Firstly, all the immunoglobulin classes are represented in the blood plasma. Thus a proportion of these proteins in lung secretions will be derived from the vascular compartment by diffusion (transudation) across the lung tissue, which behaves as a semipermeable membrane with respect to proteins in solution. The transudation rate of a protein, and hence the secretion concentration, will depend on three factors: the "resistance" of the tissues to protein diffusion, the plasma concentration of the protein, and the effective size of the protein. We do not know whether the diffusion rate of proteins across the lung varies in different anatomical areas, although local inflammation undoubtedly results in increased transudation.[1] Several proteins in lung secretions are derived exclusively by diffusion from the blood. For these proteins a correlation is observed between the secretion:serum concentration ratios and their effective sizes (expressed as Stokes' radius).[1] Consequently, if the secretion concentration of a protein (relative to that in the serum) is higher than predicted for this size, simple transduration from the blood is not the only source.

The second possible source of a protein in the lung secretions is local production by cells within lung tissues. Synthesis might be effected by cells actually within the secretions. Alternatively, proteins may be synthesised by the epithelium or cells in the lamina propria and then either diffuse or become actively transported across the epithelium.

There is now evidence to suggest that, apart from IgD, for which no data are yet available, all the immunoglobulins enter the lung secretions by all of these mechanisms.

IgA
IgA is the predominant immunoglobulin class in lung secretions in contrast to blood plasma, where IgG is found at higher concentrations. Most of the IgA in the blood (about 90%) is monomer (mIgA),[2] whereas in lung secretions about half the IgA is dimeric (dIgA) and most of this is in the form of secretory IgA (sIgA).[3] Two subclasses of IgA, IgA1 and IgA2, have been distinguished in serum and secretions by the use of specific antibodies. In the blood IgA2 comprises 10–20% of the total IgA but in bronchoalveolar lavage fluid samples it represents about 30%.[4] These differences in the IgA composition of serum and lung secretions reflect the considerable local synthesis of IgA within the lung, although a proportion of the IgA in lung secretions is still derived from the blood by transudation.[1]

Dimeric IgA (dIgA), which is produced by plasma

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cells in the lamina propria, comprises two IgA molecules linked by another protein, J chain, which is also synthesised by plasma cells. The dIgA is bound by a receptor, secretory component (SC), which is a protein inserted in the plasma membrane on the basolateral surfaces of some mucosal epithelial cells. The dIgA-SC complex on the epithelial plasma membrane is thought to be endocytosed, transported in vesicles across the cell, and released at the luminal surface as sIgA.[5]

This SC mediated transport of dIgA has been defined mainly in studies of the gut mucosa. The high concentrations of sIgA in lung secretions support the hypothesis that this mechanism also operates in the lung. Furthermore, immunohistochemical studies have shown that SC and IgA are both present on the epithelial surface, within vesicles of bronchial glandular epithelial cells and in the glandular lumen. In contrast, cilated epithelium stains only faintly for SC and is negative for IgA.[6] This evidence supports the concept of SC mediated transport of dIgA, as sIgA, across the glandular epithelium of bronchi. Secretory component and IgA associated with J chain (suggesting that the IgA is dimeric) have also been located on the plasma membrane and within pinocytic invaginations and vesicles of bronchiolar non-cilated epithelium and type II alveolar cells.[7] These results showed that SC mediated transport of dIgA could also contribute appreciably to sIgA in the lower respiratory tract.

IgA producing plasma cells are more abundant in the glands and lamina propria of major bronchi than in the small bronchi, bronchioles, or alveolar septae.[7 8] These observations suggest that most sIgA production should occur in the upper respiratory tract. This is supported by a study in dogs that showed that sIgA concentrations were highest in secretions from the upper respiratory tract.[9] Another investigation,[10] which compared the IgA components in sputum, bronchial washings, and bronchoalveolar lavage fluid from patients with chronic bronchitis, highlighted the major problem with this kind of study. The differential dilution of secretions, caused by sampling techniques, makes comparison of protein concentrations in secretions from different levels of the bronchial tree complicated.

Plasma cells in the lamina propria are not the exclusive source of sIgA in the upper or lower respiratory tract. About 10% of plasma IgA is dimeric and Haimoto et al[7] showed that IgA is present in endocytic vesicles of capillary endothelial cells, in the intercellular spaces adjoining endothelial cells, and on basement membrane. Some of this IgA was dimeric since J chain was also located in these areas. These results suggested that dIgA in capillary blood might be transported by SC into lung secretions.

Since most of the blood IgA is monomeric, a large proportion of mIgA in lung secretions should, theoretically, be derived from the plasma by transudation. Nevertheless, lung secretion concentrations of mIgA are also higher than would be predicted if the protein were derived only from the blood.[3 11] This suggests that most of the mIgA in bronchoalveolar lavage fluid and sputum is locally synthesised by plasma cells within the lamina propria, although, in contrast to dIgA, monomer is not transported across the epithelium by the SC mediated mechanism. Immunoglobulin secreting cells are also located in the mucosal secretions lining respiratory epithelium but one study of these cells, obtained by bronchoalveolar lavage, suggested that they do not contribute appreciably to the IgA found in secretions.[12]

Further evidence for local IgA synthesis in the lung has been obtained from studies of the IgA subclasses. The proportion of IgA present as IgA2 is higher in lung secretions than in blood plasma.[4] This suggests that the proportion of IgA2 producing plasma cells of the lung should be higher than that of non-mucosal lymphoid tissue. Immunohistochemical studies using antisera specific for IgA1 or IgA2 confirm this prediction. In bone marrow, tonsil, and peripheral lymph nodes 10–20% of the IgA plasma cells produce IgA2.[13 14] By comparison, 26–33% of the IgA plasma cells in bronchial mucosa produce IgA2.[13] The proportion of IgA2 in blood or lung secretions therefore reflects the proportion of IgA2 producing plasma cells in non-mucosal lymphoid tissue and bronchial mucosa respectively.

IgG

IgG is the predominant immunoglobulin class in blood and some of the lung IgG is derived from the plasma by transudation. Four subclasses of IgG have been described and each has been detected in bronchoalveolar lavage fluid samples from normal subjects.[15] In that study IgG subclass concentrations were related to albumin measurements and the IgG subclass:albumin ratios in the bronchoalveolar lavage fluid and serum samples were compared. It was concluded that IgG1 and IgG2 were derived wholly from the blood because the IgG:albumin ratios were similar in serum and lavage samples. This result, however, would actually argue in favour of an appreciable degree of local production of IgG1 and IgG2 within the lung since it does not take into account the different diffusion rates of albumin and IgG through biological tissues. Albumin, which has a Stokes radius (Rs) of 3.5 nm, is smaller than IgG (Rs = 5.1 nm) and can therefore diffuse more easily from blood to secretions. Indeed, it has been shown that if IgG were derived exclusively from the blood, the secretion:serum concentration ratio relative to that for

albumin would have a value of 0.5.[1] Any value greater than 0.5 therefore indicates a degree of local production. The secretion:serum ratio of IgG1 and IgG2, relative to albumin, reported by Merrill et al[15] approached 1.0, confirming significantly higher concentrations in bronchoalveolar lavage fluid than could be accounted for by transudation from the blood. The results reported for IgG3 and IgG4 indicated that these subclasses are also locally produced in the lung but to a relatively greater degree than IgG1 and IgG2.

Plasma cells producing IgG have been located in bronchial mucosa[8 16] and these are likely to be the source of the locally produced IgG, since IgG producing cells isolated from secretions obtained by bronchoalveolar lavage probably do not normally contribute appreciably to the concentrations of this immunoglobulin in secretions.[12] IgG synthesised by plasma cells in the bronchial mucosa will not, however, be actively transported by SC and its movement across the epithelium probably still relies on passive diffusion.

Local production of IgG3 and IgG4 is relatively greater than that of IgG1 and IgG2[15] and therefore plasma cells producing IgG3 and IgG4 are also likely to be relatively more frequent in the bronchial mucosa. Such a finding would support the idea of selective production of these subclasses. No data are yet available, however, regarding IgG subclass producing plasma cells within the lung. Further studies will be necessary to test this possibility and clarify the mechanism for IgG production in pulmonary tissues.

IgM

IgM is composed of five immunoglobulin subunits linked by a J chain and is consequently a large protein (molecular weight 900 000). Diffusion of IgM into lung secretions from the blood is greatly restricted by its large size. Nevertheless, the concentrations of IgM in bronchoalveolar lavage samples from normal subjects and sputum from bronchitic subjects are higher than can be explained by simple diffusion from the blood.[1 11] As an illustration, in bronchoalveolar lavage fluid the concentrations of IgM (relative to albumin) are higher than those of the smaller protein α_2 macroglobulin.[11] IgM producing plasma cells are present in the bronchial mucosa, though less frequently than IgG or IgA producing cells.[16] IgM is bound and transported across epithelial cells by SC and this mechanism is therefore likely to contribute appreciably to concentrations of this protein in lung secretions.

IgE

IgE is present at low concentrations in serum and bronchoalveolar lavage fluid from normal subjects.[15] The concentrations of this immunoglobulin in bronchoalveolar lavage fluid suggested appreciable local synthesis, probably by IgE producing plasma cells in the bronchial mucosa.[16]

Immunoglobulin functions in the lung

The primary function of all immunoglobulins is the recognition and binding of specific antigenic determinants, whether soluble (including toxins), particulate, or cellular, such as pathogens. The consequences of immunoglobulin binding depend on the nature of the antigen and, at its simplest, may be the physical prevention of antigen penetration through the epithelium. The secondary effects may include complement activation with target cell lysis, opsonisation resulting in enhanced phagocytosis, or antibody dependent cell mediated cytotoxicity by a variety of effector cells. The ability to intiate these secondary effects, however, varies with the immunoglobulin class and subclass concerned.

Functions of IgA

The presence of high concentrations of IgA in lung secretion suggests that this immunoglobulin class should have an important role in the neutralisation of inhaled antigens or pathogens and their toxic products. The complex structure of secretory IgA (sIgA) may in itself confer advantages on this immunoglobulin. Firstly, since sIgA has four antigen binding sites, it may be an effective agglutinating antibody, preventing bacterial growth[17] and bacterial adherence to the epithelium.[18] Secondly, secretory component has the ability to stabilise the genetic variant Am2 of the IgA2 subclass. The Am2 form is unstable since it lacks disulphide bridges between the heavy and light chains but human SC has been shown to bind dimeric and monomeric IgAm2 molecules, thus preventing their dissociation.[19] It was shown that the stabilisation of IgAm2 required an excess of SC in the reaction mixture. Free SC is present in lung secretions[20] and this mechanism might therefore occur in vivo.

The structural integrity of immunoglobulins in the lung secretions is an important requirement for their antibody activity. Lung infection and inflammation are often associated with the presence of proteinases derived from leucocytes and bacteria. It has been shown that the opsonic effect of IgG antibodies to *Pseudomonas aeruginosa* was reduced in bronchoalveolar lavage samples from patients with cystic fibrosis.[21] This inactivity of the IgG antibodies was attributed to the presence of proteinases that fragmented the immunoglobulin molecules. The concept of proteinase mediated damage to immunoglobulins

may have relevance to the presence of high concentrations of IgA2 in the lung secretions. IgA1 is susceptible to hydrolysis by proteinases produced by many pathogenic bacteria, cleavage of the IgA1 occurring at a Pro-Thr bond in the hinge region of the heavy chain.[22] IgA2 has a 13 amino acid deletion including the susceptible Pro-Thr residues. IgA2 is therefore resistant to proteolytic cleavage and its function in lung secretions would be better maintained in the presence of potentially damaging enzymes.

The ability of IgA to activate complement has been the subject of controversy. Several studies have shown that, under appropriate conditions, in vitro, IgA may be effective in activating complement by the classical or alternative pathways. The significance of these effects in vivo is, however, still unresolved and further studies are required. Similarly, there have been conflicting results regarding the opsonising ability of IgA antibodies. Secretory IgA has been shown to enhance phagocytosis by mouse alveolar macrophages,[23] but IgA antibodies to Haemophilus influenzae from bronchoalveolar lavage samples were also shown to block the opsonising activity of IgG antibodies.[24] Furthermore, although sIgA antibodies alone may not induce antibody dependent cell mediated cytotoxicity by effector cells, they have been shown to synergise with IgG in stimulating this mechanism of target cell lysis.[25] Clearly, the opsonising ability of IgA may be dependent on experimental conditions in vitro and factors such as the presence of other immunoglobulins and effector cell subpopulations should be considered. Further studies investigating the biological significance of IgA under conditions occurring in vivo may clarify our understanding of its function.

Functions of IgG
The biological effects of IgG vary considerably with the subclass concerned. Whereas IgG1, IgG2, and IgG3 can activate complement via the classical pathway, IgG4 is ineffective. The opsonising activity of an antibody will depend largely on the presence of relevant Fc receptors on effector cells. Naegel *et al*[26] showed that about 25% of human alveolar macrophages could bind IgG3 and 10% bound IgG4, whereas no significant binding of IgG1 or IgG2 was observed. These results suggest therefore that IgG3 and IgG4 may be the most important subclasses concerned in the opsonisation of pathogens for alveolar macrophages and may explain the relatively high degree of local synthesis of these proteins. Further studies will be necessary to clarify the role of IgG in inducing opsonisation by other effector cell populations in lung secretions.

Another factor to be considered is the class or subclass specific response to stimulation by particular antigens. Polysaccharide antigens appear to evoke a predominantly IgG2 response systemically,[27] whereas protein antigens favour the production of IgG1 and IgG3 antibodies.[28]

The biological effects of IgG antibodies in the lung are far from understood. Many factors, including the nature of the stimulating agents, antigen presenting cell populations, and cooperating T-cells within the lung will influence the type of antibody response. In turn, the effects of the antibodies produced will depend in part on the effector cell populations present. Since many of these cells are now recognised as being phenotypically variable in different tissues, future studies may be more rewarding if the experiments investigate appropriate human lung material.

Functions of IgM
IgM is the most effective complement fixing immunoglobulin class and the 10 antigen binding sites on the pentameric structure ensure that it is a good agglutinating antibody. IgM is the first immunoglobulin to be detected in the blood during the primary and secondary antibody responses and its main role is generally considered to be the neutralisation of pathogens, especially viruses, in the vascular compartment. The role of IgM in the lung secretions is less well understood, although its ability to activate complement and opsonise pathogens is likely to be of major importance. It is thought that IgM may be necessary in replacing the functions of IgA in subjects with selective IgA deficiency. This conclusion is based on the observation that IgM producing plasma cells and IgM concentrations in secretions were shown to be raised in the intestine of patients with IgA deficiency.[29] The relevance of these observations to the lung is not known.

Functions of IgE
IgE is bound by Fc receptors on mast cells. Cross bridging of the cell bound IgE with specific antigen results in the release of several active substances from the mast cell, including histamine and slow reacting substance of anaphylaxis (leukotrienes C4, D4, and E4), which result in bronchiolar smooth muscle contraction and increased blood vessel permeability. The mast cells also release potent enzymes, including elastase, cathepsin G, and kininogenase.[30][31] Furthermore, other cells are recruited to the inflammatory process through the release of neutrophil and eosinophil chemotactic factors and platelet activating factor. This IgE mediated inflammatory response is most evident in type 1 hypersensitivity reactions such as occur in allergic asthma, but it has been proposed that this mechanism has an important role in the host defence against metazoan parasites.[32] In addition,

IgE may itself interact with other inflammatory cells. For instance, IgE has been shown to bind to receptors on alveolar macrophages causing the release of lysosomal enzymes.[32]

The factors responsible for high IgE antibody concentrations in atopic individuals are not known, although defects in T cell function have been suggested.[33]

Disease and lung immunoglobulins

The immunoglobulin composition of the lung may be influenced by many factors. In some diseases, however, the aetiology or progression of the condition appears to be directly related to abnormal immunoglobulin production or function. Thus autoantibodies may be an important feature in Goodpastures's disease and atopy is often associated with excessive IgE synthesis. The present discussion, however, will be confined to two groups of lung diseases, the interstitial and obstructive lung conditions.

Interstitial lung diseases
The interstitial lung diseases are characterised by infiltration of the interstitium by inflammatory cells and the development of alveolitis, fibrotic changes, and granulomas. There appears to be a significant "immunological" component to the pathogenesis of these diseases, indicated by the presence of activated T lymphocytes and a polyclonal stimulation of immunoglobulin synthesis, including autoantibodies.[34] Sarcoidosis is associated with a significant increase in serum concentrations of IgA and a significant, though small, increase in serum IgG.[12]

The most striking changes in immunoglobulin production in interstitial diseases are revealed by the analysis of lung secretions from patients with these conditions. Several studies have shown greater IgG and IgA concentrations in bronchoalveolar lavage fluid samples from patients with sarcoidosis than in samples from healthy controls.[11 12 35] The concentration of IgM in lavage fluid in sarcoidosis was also shown to be increased in two of these studies[11 35] but was reported to be similar to that in lavage fluid from controls by Rankin et al.[12] The increased immunoglobulin concentrations in lavage fluid were related to disease activity since they were observed only in patients with high intensity alveolitis,[11 35] and clinical improvement after corticosteroid treatment was associated with reduced immunoglobulin concentrations in lavage fluid.[35]

Idiopathic pulmonary fibrosis, fibrosing alveolitis, and chronic hypersensitivity pneumonitis were also reported to be associated with increased concen-

trations of IgG and IgA in lavage fluid.[36] IgM was also increased in chronic hypersensitivity pneumonitis but no significant increase in IgE concentrations in lavage fluid were observed. This study also showed a significant reduction in IgG in lavage fluid after corticosteroid treatment.

The increased immunoglobulin concentrations in the lung secretions of patients with interstitial lung disease would appear to occur for two reasons. The first is an increase in the transudation of protein from the blood, presumably because of inflammation within the lung. This conclusion is based on the observation that albumin concentrations in lavage fluid are also frequently increased in sarcoidosis,[11 12] although not in idiopathic pulmonary fibrosis.[36] Secondly, local synthesis of immunoglobulins is likely to result from an increase in synthesis by plasma cells in the lung, including cells within the secretions lining the airways. Although no significant relationship was observed between the number of immunoglobulin secreting cells and immunoglobulin levels in bronchoalveolar lavage fluid from normal subjects, a correlation was reported for IgG (but not IgA or IgM) in lavage fluid from patients with sarcoidosis.[12] Other studies have reported an increase in IgG secreting cells in lavage samples from patients with sarcoidosis[34 37] and idiopathic pulmonary fibrosis.[37] The results were not conclusive for other immunoglobulins since Hunninghake and Crystal[34] observed an increase in IgM producing cells in lavage samples from patients with sarcoidosis but Lawrence et al[37] reported no difference in comparison with controls. No increase in IgA secreting cells were found. Interestingly, successful corticosteroid treatment reduced the numbers of IgG producing cells in lavage samples from the patients with sarcoidosis.[37] The increased immunoglobulin concentrations in lung secretions from patients with interstitial lung disease clearly result mainly from local synthesis by plasma cells and, by contrast with the normal lung, a considerable proportion of this protein is derived from cells lining the airways. The source of these cells is not known. The predominant form (80%) of IgA in bronchoalveolar lavage fluid from subjects with sarcoidosis, however, is monomer.[11] Since this represents a higher proportion of monomer than is present in the normal lung, it was suggested that the plasma cells responsible for IgA synthesis in the sarcoid lung were recruited from the blood.[11] Alternatively, subpopulations of B lymphocytes already within the lung could be stimulated in these diseases. This explanation seems less likely in view of the polyclonal nature of the immunoglobulins produced.[34]

The reasons for the increased synthesis of immunoglobulins in patients with interstitial lung diseases remains obscure. The phenomenon appears to be

localised specifically to the lung. This is supported by the observed increase in immunoglobulin concentration and number of immunoglobulin producing cells in bronchoalveolar lavage fluid samples and by the increase in numbers of T helper cells in the lung secretions obtained from patients with interstitial lung diseases. Furthermore, T cell numbers correlated with immunoglobulin concentrations and number of immunoglobulin producing plasma cells and with disease activity.[34][35] Perhaps most important was the observation that these T cells could induce immunoglobulin synthesis in otherwise unstimulated B cells from the blood of normal individuals.[34] The evidence so far therefore suggests that T cell mediated synthesis of immunoglobulins within the lung is a central feature of interstitial lung diseases. The mechanisms leading on to lung damage are not yet clear. Further identification of the subpopulations of the immunoglobulins produced in these conditions would be interesting. This might help to establish whether there is a functional association between the immunoglobulins, effector cells, and pathological changes seen in the lungs.

Infections and obstructive lung disease

Immunoglobulin deficiencies are often associated with chronic or recurrent pulmonary infections and several studies have investigated the immunoglobulin class or subclass deficiencies in the serum of patients with these respiratory problems. The frequency of observed immunoglobulin deficiencies in these patients differ considerably from study to study and will reflect the groups of patient selected. For instance, the frequency of selective serum IgA deficiency (< 50 mg/l) in caucasians is 1/300–1/2000 but in the Japanese population it is much rarer, having an incidence of only 1/18 000.[38] Furthermore, the specificity of the assays used will dictate whether an immunoglobulin deficiency is detected. Serum deficiencies of IgG clearly are often overlooked unless the IgG subclasses are quantified. For instance, Umetsu *et al*[39] studied 20 children with recurrent sinopulmonary infections who had normal total serum IgG concentrations. All of these children were, however, deficient in one or more IgG subclass and 15% were deficient in IgA. The most frequent IgG subclass deficiency was IgG2, and this was possibly the reason for the observed low titres of antibody to the capsular polysaccharide of *Haemophilus influenzae* in these patients.

Studies in other groups of patients have detected lower frequencies of immunoglobulin deficiencies in the serum of patients with recurrent and chronic chest infections.[40] Furthermore, in some patients immunoglobulin concentrations were increased in response to

the microbial antigen challenge.

Several factors may explain why immunoglobulin deficiency has not been detected in many patients with chronic or recurrent infections. Firstly, the recognised incidence of immunoglobulin deficiency has increased since assays for IgG subclasses were introduced. More specific assays for the measurement of IgA subclasses and antigen specific antibodies might reveal further causes of infection. Secondly, despite normal immunoglobulin concentrations, deficiencies in effector cell function may be present in a proportion of patients. Thirdly, and relevant to all of these possibilities, is the need to quantify the components of the immune system in the lungs of these patients rather than in the serum. Infections are often confined to the lungs, and thus deficiencies in local immunoglobulin synthesis alone may be a key aetiological factor. For instance, specific sIgA deficiency has been described in patients with normal serum IgA concentrations.[20] The secretory IgA system may therefore be independent of the systemic IgA system, and this might also be the case for other immunoglobulins. At present little is known about how the immunoglobulin composition of the lung secretions of patients with recurrent or chronic respiratory infections compares with that of normal individuals.

The IgA system has been studied in sputum samples obtained from patients with chronic bronchitis. In those who were not apparently IgA deficient the presence of a clinical pulmonary infection was associated with significantly increased sputum mIgA and dIgA.[3] An appreciable amount of the IgA (both monomer and dimer) was locally synthesised, presumably in response to the infecting organisms. These results suggest that the lungs of most patients with chronic bronchitis are capable of mounting an IgA immune response to infecting organisms, although no comparison with the healthy lung is yet possible.

Soutar[8] reported that patients who had died from chronic obstructive bronchitis were deficient in IgA producing plasma cells throughout the respiratory tract, whereas patients with bronchitis who had died of other causes were normal, which suggests that fatal bronchitis was associated with a deficiency of lung IgA plasma cells. A more recent study reported increased IgA plasma cells in the bronchi of patients with chronic bronchitis.[41] The plasma cells were of both IgA subclasses but the increase was mainly in the plasma cells producing IgA1. Clearly these different results may be explained in part by the study of different groups of patients. Further studies are required, quantifying the IgA and IgG subclasses in bronchoalveolar lavage fluid from patients with chronic obstructive lung disease and comparing the concentrations with those of normal individuals. Such comparisons will clarify whether immuno-

globulin deficiencies have a role in the aetiology of chronic obstructive lung disease.

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